Lactic acid promotes PD-1 expression in regulatory T cells in highly glycolytic tumor microenvironments

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Highlights

- Lactic acid (LA) induces PD-1 expression by Treg cells in highly glycolytic tumors.
- LA absorbed through MCT1 is a metabolic checkpoint of immune responses.
- MYC expression accelerates glycolysis and promotes PD-1 expression by Treg cells.
- MCT1 highly expressed by Treg cells, provides therapeutic target for immunotherapy.

Summary

High PD-1 expression by Treg cells in the tumor microenvironment (TME) is a resistant mechanism for PD-1 blockade therapy. Treg cells harbor higher PD-1 expression compared to effector T cells in highly glycolytic tumors including MYC-amplified tumors and liver tumors. Mechanistically, under low-glucose environments, tumors release a large amount of LA that is taken up by Treg cells through MCT1, the expression of which is controlled by FOXP3 and promotes NFAT1 translocation into the nucleus, resulting in enhanced PD-1 expression by Treg cells but not effector T cells. Kumagai et al. propose a novel mechanism of PD-1 expression by Treg cells induced by LA through MCT1 in highly glycolytic tumors, thereby playing an active role in the impairment of antitumor immunity and the resistance to PD-1 blockade therapy.

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